

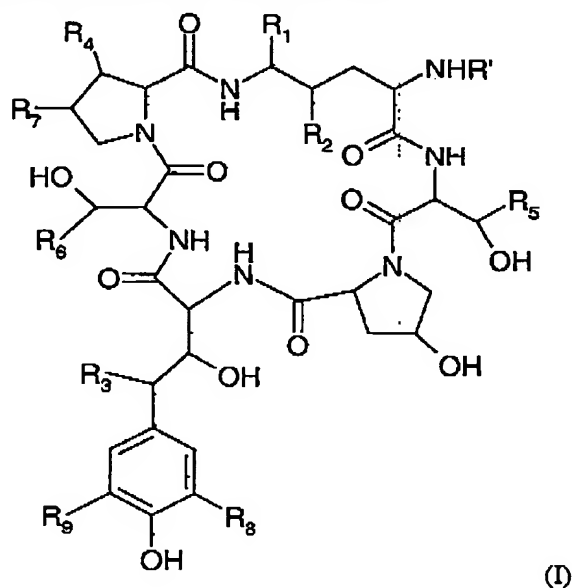
Application Ser. No.: 10/031,764
 Filing Date: September 30, 2002
 Examiner: Audet, Maury A.

Amendment Pursuant to 37 C.F.R. § 1.121

IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

1. (currently amended) A compound selected from the group consisting of a cyclohexapeptide compound of the formula (I).



wherein,

R' is selected from the group consisting of C₉-C₂₀ alkyl; C₉-C₂₀ alkenyl; C₉-C₂₀ alkoxyphenyl, phenyl, biphenyl, terphenyl, and naphthyl; C₁-C₁₂ alkylphenyl, C₈-C₁₂ alkenylphenyl, C₁-C₁₂ alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; and COC₆H₄(p)OC₈H₁₇,

R₁ is selected from the group consisting of -CN; -CH₂NH₂; -N₃; aryl; substituted aryl; imidazolyl; morpholinoethylamino; -OR, wherein R is C₄-C₁₂ alkyl; C₁-C₁₂ alkyl, substituted alkyl of (CH₂)_n-X, where n is 1-5 and X is selected from the

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group consisting of OH, aryl, Cl, Br, I, COOY and CN, wherein Y is selected from the group consisting of C₁-C₆ alkyl, C₂-C₁₂ alkenyl, aryl, fused aryl, substituted aryl, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl and a hydroxy protecting group;

R₃ is selected from the group consisting of -OH; -CN; -CH₂NH₂; -N₃; aryl; substituted aryl; heterocyclyl and substituted heterocyclyl with 1-3 of heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; imidazolyl; -OR, wherein R is C₁-C₁₂ alkyl; substituted alkyl of (CH₂)_n-X, where n is 1-5 and X is selected from the group consisting of OH, aryl, Cl, Br, I, COOY, CN, NH₂ and heterocyclic, wherein Y is selected from the group consisting of C₁-C₆ alkyl, C₂-C₁₂ alkenyl, aryl, fused aryl, substituted aryl, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, and a hydroxy protecting group;

R₂ and R₄ are independently -H or -OH;

R₅ is -H or -CH₃;

R₆ is selected from the group consisting of -H, -CH₃ and -CH₂CONH₂;

R₇ is selected from the group consisting of -H, -CH₃ and -OH;

R₈ and R₉ are independently -H or -CH₂-Sec.amine in which the sec.amine is attached to -CH₂ through its N linkage; with the proviso that both R₈ and R₉ are not simultaneously hydrogen;
and its non-toxic pharmaceutically acceptable salts.

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2. (previously presented) The compound of claim 1 wherein R_1 is OR, and R_3 is selected from the group consisting of -OH, -OR and imidazolyl wherein R in each case is selected from the group consisting of C_1 - C_{12} alkyl, substituted alkyl of $-(CH_2)_n-X$, where n is 1-5, X is selected from the group consisting of OH, aryl, Cl, Br, I, COOY and CN, and wherein Y is selected from the group consisting of C_1 - C_6 alkyl, C_2 - C_{12} -alkenyl, aryl, fused aryl, substituted aryl, a heteroaryl containing 1-3 heteroatoms, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl and a hydroxy protecting group.
3. (previously presented) The compound of claim 1 wherein R' is selected from the group consisting of linoleoyl, palmitoyl, 12-methylmyristoyl, 10,12-dimethylmyristoyl and $-COC_6H_4(p)OC_8H_{17}$.
4. (previously presented) The compound of claim 1 wherein 1) to the nitrogen atom of the secondary amine are attached at least one member of the group consisting of C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or 2) the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by at least one member of the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkenyl, aryl, amino, nitro, and halogen, or 3) the nitrogen atom of the secondary amine is part of a fused heterocyclic group, wherein the heterocyclic group contains 1-3 heteroatoms.
5. (previously presented) The compound of claim 1 wherein the secondary amine is selected from the group consisting of piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamine, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α -trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl)piperazine,

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1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tertbutyl)benzylamine and N-(isopropyl)-benzylamine.

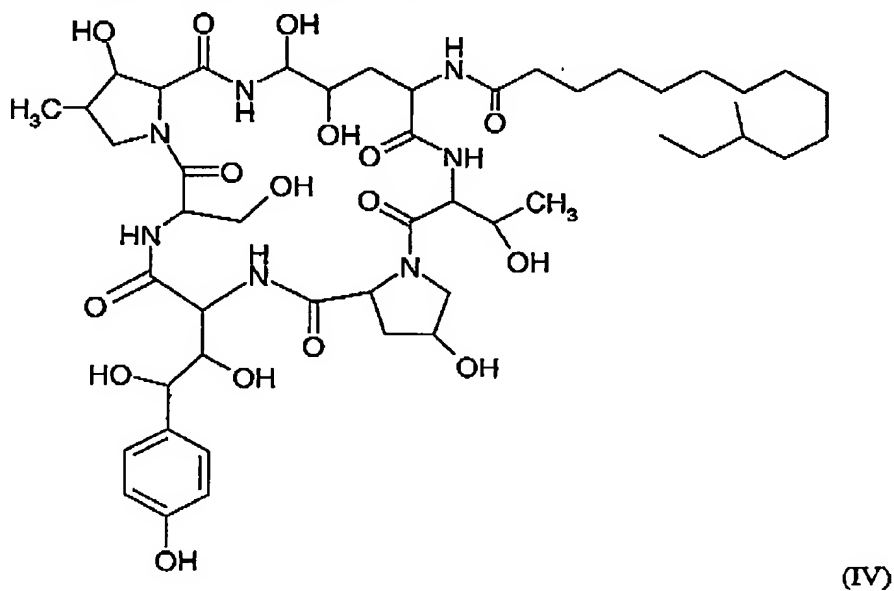
6. (currently amended) The compound of claim 1, wherein R' is 12-methylmyristoyl, R₁ is selected from the group consisting of -CN, -CH₂NH₂, -N₃, aryl, substituted aryl, -OCH₂C₆H₄, -OCH₃, -OCH₂OH, morpholinoethylamino and imidazolyl R₃ is selected from the group consisting of -OH, -CN, -CH₂NH₂, -N₃, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl having 1-3 heteroatoms, aminoalkylamino, and mono or di-substituted linear or cyclic aminoalkylamino, R₅ and R₇ are both -CH₃, and R₆ is -H, ~~and R₈ and R₉ are both -H.~~
7. (original) An antifungal composition comprising a fungicidally effective amount of a compound of claim 1, and a non-toxic pharmaceutically acceptable carrier.
8. cancelled.
9. (previously presented) A process for the production of a compound of claim 1 comprising:
- a) reacting a cyclohexapeptide compound of claim 1, wherein R', R₂, R₄, R₅, R₆ and R₇ are as defined in claim 1, R₁ and R₃ are both -OH, and R₈ and R₉ are -H, with an alcohol in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60°C to obtain the corresponding cyclohexapeptide derivative of claim 1 wherein R', R₂, R₄, R₅, R₆ and R₇ are as defined in claim 1, R₁ and R₃ are independently -OH or -OR wherein at least one of R₁ or R₃ is -OR, R is selected from the group consisting of C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl; and a hydroxy protecting group, and R₈ and R₉ are -H;

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- b) reacting the compound of step (a) with a secondary amine in the presence of paraformaldehyde in an aprotic solvent at a temperature of 60°C to 150°C to obtain the desired compound of formula I, isolating and purifying the resulting compound from the reaction mixture in a known manner and optionally converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

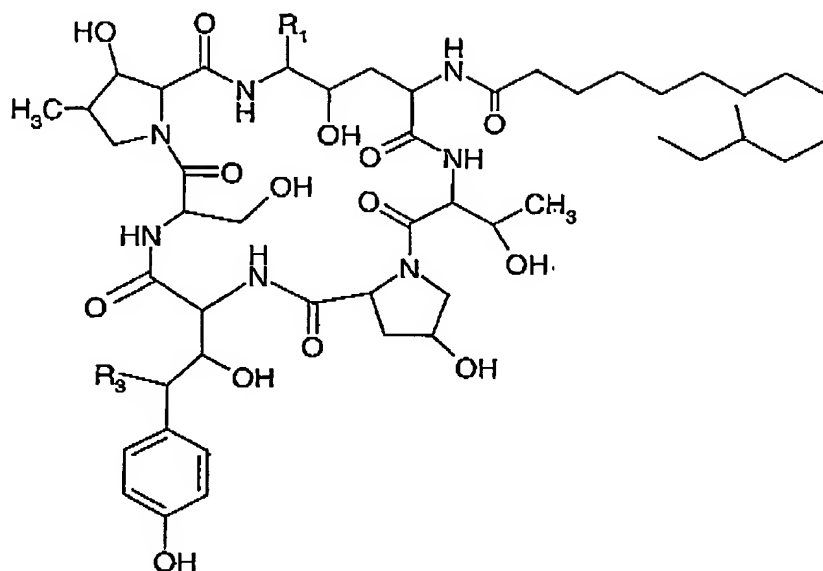
10. (currently amended) A process for the preparation of a cyclohexapeptide compound of claim 1 comprising:

- a) reacting mulundocandin of the formula



with a nucleophile in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60°C to obtain the corresponding cyclohexapeptide derivative of the formula

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(V)

wherein R_1 and R_3 are $-OH$ or $-SR$ with at least one of R_1 or R_3 is $-SR$, R is selected from the group consisting of C_1 - C_{12} alkyl, substituted alkyl of $-(CH_2)_n-X$, where n is 1-5, X is Cl, Br, I, $COOY$, CN, NH_2 and a heterocyclic, Y is selected from the group consisting of C_1 - C_6 alkyl; C_2 - C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;

- b) reacting the compound of step (a) with an oxidizing agent in an aqueous medium at a temperature of $20^\circ C$ to $60^\circ C$ to obtain the corresponding sulfones of formula V wherein R_1 and R_3 are $-OH$ or $-S(O_2)R$, with at least one of R_1 or R_3 is $-SO_2R$, R is selected from the group consisting of C_1 - C_{12} alkyl, substituted alkyl of $-(CH_2)_n-X$, where n is 1-5, X is Cl, Br, I, $COOY$, CN, NH_2 and a heterocyclic, Y is selected from the group consisting of C_1 - C_6 alkyl; C_2 - C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;

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- c) reacting the sulfone of step(b) with a ~~nucleophile~~ secondary amine in a solvent at a temperature of 20°C to 60°C to obtain the desired compound of claim 1, isolating and purifying the resulting compound and optionally converting the compound of claim 1 into its pharmaceutically acceptable salt in a known manner.